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Global Differences in Burden and Treatment of Ischemic Heart Disease in Acute Heart Failure

REPORT-HF

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ABSTRACT

OBJECTIVES The primary aim of the current study was to investigate global differences in prevalence, association with outcome, and treatment of ischemic heart disease (IHD) in patients with acute heart failure (AHF) in the REPORT-HF (International Registry to Assess Medical Practice With Longitudinal Observation for Treatment of Heart Failure) registry.

BACKGROUND Data on IHD in patients with AHF are primarily from Western Europe and North America. Little is known about global differences in treatment and prognosis of patients with IHD and AHF.

METHODS A total of 18,539 patients with AHF were prospectively enrolled from 44 countries and 365 centers in the REPORT-HF registry. Patients with a history of coronary artery disease, an ischemic event causing admission for AHF, or coronary revascularization were classified as IHD. Clinical characteristics, treatment, and outcomes of patients with and without IHD were explored.

RESULTS Compared with 8,766 (47%) patients without IHD, 9,773 (53%) patients with IHD were older, more likely to have a left ventricular ejection fraction <40% (heart failure with reduced ejection fraction [HFrEF]), and reported more comorbidities. IHD was more common in lower income compared with high-income countries (61% vs. 48%). Patients with IHD from countries with low health care expenditure per capita or without health insurance less likely underwent coronary revascularization or used anticoagulants at discharge. IHD was independently associated with worse cardiovascular death (hazard ratio: 1.21; 95% confidence interval: 1.09 to 1.35). The association between IHD and cardiovascular death was stronger in HFrEF compared with heart failure with preserved ejection fraction ($p_{\text{interaction}} < 0.001$).

CONCLUSIONS In this large global contemporary cohort of patients with AHF, IHD was more common in low-income countries and conveyed worse 1-year mortality, especially in HFrEF. Patients in regions with the greatest burden of IHD were less likely to receive coronary revascularization and treatment for IHD. (J Am Coll Cardiol HF 2021;9:349–59)

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**ABBREVIATIONS
AND ACRONYMS****ACS** = acute coronary syndrome**ACE** = angiotensin-converting enzyme inhibitor**AHF** = acute heart failure**ARB** = angiotensin receptor blocker**CABG** = coronary artery bypass grafting**CAD** = coronary artery disease**CI** = confidence interval**CV** = cardiovascular**HFmrEF** = heart failure with mid-range ejection fraction**HFpEF** = heart failure with preserved ejection fraction**HFrEF** = heart failure with reduced ejection fraction**HR** = hazard ratio**IHD** = ischemic heart disease**LASSO** = least absolute shrinkage and selection operator**MI** = myocardial infarction**NYHA** = New York Heart Association**OR** = odds ratio**PCI** = percutaneous coronary intervention

Ischemic heart disease (IHD) is a common cause of heart failure (HF) (1) and is associated with increased mortality (1–3). Although the prevalence of risk factors for developing IHD is lower in low-income countries, the relative incidence and case-fatality rate of IHD is often higher. This is possibly caused by a combination of poor risk factor control and worse health system quality (4,5).

In the INTER-CHF (International Congestive Heart Failure) study, IHD was the primary etiology in 56% of patients with HF from Southeast Asia and in 45% of patients in China (6). In the European Society of Cardiology long-term registry (7), the prevalence of IHD was highest in Eastern Europe at 47%. However, both studies included a limited number of countries, and no study investigated the global burden and treatment of IHD in patients with HF in a prospective contemporary cohort.

REPORT-HF (International Registry to Assess Medical Practice With Longitudinal Observation for Treatment of Heart Failure) is a global, prospective, and observational cohort study uniquely designed to assess differences in comorbidities and treatment of patients hospitalized for HF (8). The primary aim of the current study was to investigate global differences in prevalence,

association with outcome, and treatment of IHD in patients with acute HF (AHF) in REPORT-HF.

METHODS

STUDY DESIGN AND SETTING. Methods, design, and 1-year outcomes of the REPORT-HF have been described elsewhere (9,10). Briefly, REPORT-HF was an observational, prospective, global cohort study with patients enrolled from 6 continents, 44 countries, and 358 sites. Eligible patients were asked to give consent and enrolled consecutively or intermittent consecutively on pre-determined days of the week or weeks of the month. The original proposed sample size was 20,000 patients to analyze all comparisons of interest with an assumed attrition of 30%. The target sample was re-evaluated when ~50% of patients were recruited during a pre-specified interim

analysis (8). This resulted in a revised estimated attrition rate of ~25%. The following adjusted sample size was 18,700 for the total cohort. Enrollment took place between July 23, 2014, and March 24, 2017.

PARTICIPANTS AND STUDY PROCEDURES. REPORT-HF was conducted in accordance with the Declaration of Helsinki, and the protocol received institutional review board and/or ethics committee approval at each participating center. All participants were hospitalized with a primary diagnosis of AHF, based on the judgment of the treating physician. Study investigators were encouraged to adhere to local standards and recommendations for the diagnosis and treatment of AHF. Written informed consent was required from all participants or a legal representative, if permitted. Patients unable or unwilling to provide consent or patients participating in a clinical trial were excluded.

Data on patients' demographic characteristics, medical history, physical examination, vital signs, laboratory values, acute therapies, hospital course, procedures, length of stay, and mortality were collected and captured in a central electronic database using the same case report form at all sites. A central data-management committee reviewed the data and raised queries where necessary. These queries were then resolved by local study monitors.

HF with reduced ejection fraction (HFrEF) was defined as a left ventricular ejection fraction (LVEF) <40%, HF with mid-range ejection fraction (HFmrEF) was defined as an LVEF 40% to 49%, and HF with preserved ejection fraction (HFpEF) was defined as an LVEF ≥50% in keeping with current guidelines (11). LVEF was assessed in 82% of patients with a reported LVEF during the index hospitalization. When this information was not available, the LVEF reported before the index hospitalization was used. IHD was defined as having a history of coronary artery disease (CAD), acute coronary syndrome (ACS) or myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary arterial bypass grafting (CABG), or ischemic etiology of HF. New-onset IHD was separately defined as having ACS/MI as a precipitant leading to hospitalization, having a PCI/CABG during the index hospitalization, or experiencing a new-onset ACS/MI during the index hospitalization (Supplemental Table 1).

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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CENTRAL ILLUSTRATION Geographic Differences in Ischemic Heart Disease

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World map showing the prevalence of ischemic heart disease per country included in REPORT-HF (International Registry to Assess Medical Practice With Longitudinal Observation for Treatment of Heart Failure).

COLLECTION OF DATA ON MEDICATION. The exact time of first administration of all intravenous treatments for AHF was recorded; the time of arrival was similarly captured and the difference between the time of arrival and time of administration was defined as the door-to-treatment time. Medication data were captured at discharge and 6 months through follow-up with the patient and/or primary care provided. Names of medical therapies, dosages, and units were captured. Queries were raised by programmed database edit if no medications were recorded, and manual review with queries were raised when doses/units were off. When no medications were recorded at follow-up visits, it was assumed that these data were missing, because it is unlikely that a patient would not be taking some medication. When one or more medications were recorded (e.g., a diuretic or hypoglycemic agent) but this did not include one or more guideline-recommended treatments for HF, it was assumed that these agents had not been prescribed. We calculated maximum daily doses attained at discharge and 6 months' follow-up among the proportion of patients

on guideline-recommended β -blockers, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists ([Supplemental Table 2](#)).

OUTCOMES. Standardized follow-up calls were performed at 6 months and 1 year. Unless a regular follow-up visit was planned at the investigator site for routine care, information from study participants was collected during telephone interviews. Vital status was supplemented by national recording databases where available. Causes of death were ascertained by the local investigators and captured as cardiovascular (CV) versus non-CV. Patients were considered lost to follow-up if no information was available on vital status or any follow-up visit. Outcomes were not independently adjudicated.

STATISTICAL ANALYSIS. Differences in patient treatment are reported according to IHD status. Stratifications were made according to country spending on health care per capita purchasing power parity provided by the World Bank, using 2017 as the reference year and country income level as reported

TABLE 1 Baseline Characteristics

	No IHD (n = 8,766)	IHD (n = 9,773)	p Value
Demographics			
Age (yrs)	65 (53-76)	69 (60-77)	<0.001
Male	4,861 (55)	6,505 (67)	<0.001
Race			<0.001
White	4,377 (50)	5,270 (54)	
Black	524 (6)	342 (3)	
Asian	2,517 (29)	3,218 (33)	
Native American	271 (3)	104 (1)	
Pacific Islander	5 (<1)	2 (<1)	
Other	1,072 (12)	837 (9)	
Region			<0.001
Central and South America	1,655 (19)	985 (10)	
Eastern Europe	999 (11)	1,803 (18)	
Eastern Mediterranean region and Africa	966 (11)	1,274 (13)	
North America	810 (9)	781 (8)	
Southeast Asia	1,006 (11)	1,321 (14)	
Western Europe	1,837 (21)	1,749 (18)	
Western Pacific	1,493 (17)	1,860 (19)	
New-onset HF	4,090 (47)	3,805 (39)	<0.001
Decompensated chronic HF	4,676 (53)	5,968 (61)	
NYHA functional class before admission			<0.001
I	408 (5)	443 (5)	
II	1,525 (17)	1,754 (18)	
III	2,298 (26)	2,780 (28)	
IV	956 (11)	1,196 (12)	
LVEF			<0.001
<40% (HF _r EF)	3,958 (45)	4,941 (51)	
40%-49% (HF _{mr} EF)	1,128 (13)	1,742 (18)	
≥50% (HF _p EF)	2,867 (33)	2,296 (23)	
Unknown	813 (9)	794 (8)	
Heart rate (beats/min)	90 (75-106)	84 (72, 100)	<0.001
Systolic blood pressure (mm Hg)	130 (110-150)	130 (114, 150)	<0.001
Diastolic blood pressure (mm Hg)	80 (69-90)	80 (69-90)	0.014
Signs and symptoms			
Dyspnea at rest	6,324 (83)	7,278 (83)	0.64
Orthopnea	5,343 (78)	6,281 (78)	0.93
Chest pain	3,152 (41)	4,918 (56)	<0.001
Peripheral edema	5,510 (71)	5,891 (67)	<0.001
Pulmonary rales	4,676 (66)	5,604 (68)	0.006
Medical history			
Hypertension	5,063 (58)	6,745 (69%)	<0.001
Atrial fibrillation/flutter	3,049 (35)	2,717 (28)	<0.001
COPD/asthma	1,179 (13)	1,476 (15)	0.001
Anemia	3,785 (43)	4,939 (51)	<0.001
Valvular heart disease	2,228 (25)	1,451 (15)	<0.001
Diabetes	2,538 (29)	4,527 (46)	<0.001
Chronic kidney disease	1,452 (17)	2,314 (24)	<0.001

Values are median (interquartile range) or n (%).

COPD = chronic obstructive pulmonary disease; HF = heart failure; HF_{mr}EF = heart failure with mid-range ejection fraction; HF_pEF = heart failure with preserved ejection fraction; HF_rEF = heart failure with reduced ejection fraction; IHD = ischemic heart disease; IQR = interquartile range; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

previously (9). In addition, the 44 participating countries were grouped. Comparisons between groups were tested by using the Student's *t*-test, chi-square test, or Mann-Whitney *U* test for normally

distributed continuous variables, categorical variables, and non-normally distributed continuous variables, respectively. Multivariable logistic regression analyses were performed to investigate factors associated with medication use. Variables were selected based on clinical significance and expert opinion. In addition, we corrected for the MAGGIC risk score (12), which includes LVEF, systolic blood pressure, age, sex, body mass index, creatinine, New York Heart Association (NYHA) functional class, history of diabetes or chronic obstructive pulmonary disease, time since diagnosis, use of ACE inhibitors/ARBs at discharge, and use of beta-blockers at discharge.

REPORT-HF was designed to assess differences in clinical practice, availability of diagnostic tests, and treatment; missingness of variables was therefore considered to be not completely at random but due to differences in local practice and availability, as previously reported (9). For the stepwise Cox model, 75 patients had missing data for any one of the variables and were removed from further analyses. Due to missingness of systolic blood pressure, body mass index, and creatinine, multiple imputation was used to calculate the MAGGIC risk score per patient. Imputation was performed by using the Multivariate Imputation by Chained Equations (MICE) package in R, using default polytomous regression for multilevel factor variables, logistic regression for binary variables, and predictive mean matching for continuous variables. Values were averaged over 5 imputation sets, and the risk score per patients was calculated based on the averaged values. For the least absolute shrinkage and selection operator (LASSO) regression analyses, variables were transformed to tertiles and included "missing" as a separate factor level. Kaplan-Meier curves were used to graphically depict differences in 1-year mortality, whereas cumulative incidence curves were used for CV mortality. In all analyses for CV and non-CV mortality, deaths classified other than the outcome were considered as a competing risk. Multivariable analyses were performed by using Cox regression analyses. The proportionality of hazards assumption was checked by using statistical tests and graphical diagnostics on the basis of the Schoenfeld residuals.

Patients without any follow-up data were excluded. Patients were censored at their date of death or last known follow-up date. To account for differences in facility level characteristics within countries, we allowed estimates of our logistic and Cox regression models to cluster around the center variable. We tested for interaction between history of IHD and HF subtype (HF_rEF, HF_{mr}EF, and HF_pEF) for 1-year all-cause mortality. In sensitivity analyses, we

restricted the test for interaction to patients with LVEF measured during the index hospitalization. To correct for treatment indication bias in outcome analyses of medication, inverse probability weighting was used. The probability of being on the drug was modeled by using LASSO penalized regression analyses based on 73 variables (Supplemental Table 3). To find the optimal lambda in the LASSO regression, 10 cross-validations were performed to increase robustness (13). Because we accounted for center effects in our logistic and survival models, we did not account for multiple testing. Due to the large sample size and small p values in most comparisons made, we view the p values considering the relative effect sizes and clinically important differences. A 2-sided p value <0.05 was considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS. Between July 23, 2014, and March 24, 2017, a total of 18,539 patients were prospectively enrolled. In total, 9,773 (53%) patients had IHD. The prevalence of IHD ranged from 22% in Ecuador to 78% in Russia. The prevalence of IHD was higher in countries such as China (56%) and India (60%) than the United States (48%). IHD was more common in Eastern Europe, Southeast Asia, and the Western Pacific (Central Illustration, Supplemental Table 4). When stratified according to country income level, the prevalence of IHD was higher ($p < 0.001$) in lower-income countries (61%) than in high-income countries (48%).

When stratified according to medical history of IHD alone, or new-onset IHD (Supplemental Table 4), 6,627 (36%) patients had a medical history of IHD and 3,146 (17%) patients had new-onset IHD. In the eastern Mediterranean and Africa region, Southeast Asia, and the Western Pacific, new-onset IHD was more common (21%, 30%, and 24%, respectively) compared with other regions.

Patients with IHD were older, more often men, less often presented with new-onset HF, had a higher NYHA functional class prior to admission, more likely a LVEF <50%, and more often had chest pain and less often peripheral edema (Table 1). A medical history of hypertension, anemia, diabetes and chronic kidney disease was more common in patients with IHD compared with those without IHD.

TREATMENT CHARACTERISTICS. Door to any intravenous treatment time, door to vasodilator time, and door to diuretic time were shorter in patients with IHD compared with those without (Table 2). After accounting for age, sex, NYHA functional class before admission, and regional income level, these

TABLE 2 In-Hospital Characteristics and 1-Year Outcomes

	No IHD	IHD	p Value
Mode of transport			<0.001
Own transport	6,077 (69)	6,317 (65)	
Ambulance	2,046 (23)	2,739 (28)	
Other	637 (7)	709 (7)	
Hospital point of entry			<0.001
Point of entry			
Emergency department	5,680 (65)	5,947 (61)	
Heart failure facilities	422 (5)	501 (5)	
Cardiac ward	1,513 (17)	1,833 (19)	
Cardiac/coronary ICU	559 (6)	893 (9)	
General/medical/surgical ICU	266 (3)	216 (2)	
Other	320 (4)	378 (4)	
Time to treatment for AHF			
Time to any (min)	60 (13-185)	53 (8-168)	<0.001
Time to IV vasodilators (min)	77 (25-255)	58 (11-202)	<0.001
Time to IV inotropics (min)	230 (45-1,728)	233 (42-2,558)	0.540
Time to IV diuretics (min)	78 (22-224)	69 (15-219)	<0.001
Discharge medication			
ACE inhibitor/ARB	5,604 (66)	6,280 (66)	0.620
GRT	5,156 (92)	5,708 (91)	0.030
Median fraction	0.5 (0.25-0.63)	0.33 (0.25-0.57)	0.001
Beta-blockers	5,971 (70)	7,063 (74)	<0.001
GRT	5,805 (97)	6,937 (98)	<0.001
Median fraction	0.25 (0.20-0.50)	0.25 (0.13-0.50)	0.052
MRA	4,247 (50)	4,599 (48)	0.057
Median fraction	0.33 (0.33-0.5)	0.33 (0.33-0.67)	<0.001
Length of stay (d)	8 (5-12)	8 (5-12)	<0.001
1-yr outcomes*			
Mortality	1,500 (18)	1,958 (21)	<0.001
Hospitalization	2,997 (36)	3,671 (39)	<0.001
Days in hospital	11 (5-23)	11 (5-22)	0.95
Hospitalization for HF	1,769 (21)	2,168 (23)	0.002
Days in hospital	10 (5-20)	10 (5-20)	0.88
CAD	177 (2)	557 (6)	<0.001
MI/ACS	46 (<1)	144 (2)	<0.001
CABG	31 (<1)	117 (1)	<0.001
PCI	84 (1)	322 (3)	<0.001

Values are n (%) or median (interquartile range). *Patient population not lost to follow-up within 1 year used as denominator.

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; CAD = coronary artery disease; GRT = guideline-recommended therapy; ICU = intensive care unit; IV = intravenous; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

associations were no longer significant (all $p > 0.10$). In total, 999 (10%) patients with IHD underwent a PCI during hospitalization and 116 (1.1%) a CABG.

In total, 72 (0.4%) patients had missing data on medication at discharge. In univariable analyses, patients from countries with lower health care expenditure more frequently underwent CABG/PCI during index hospitalization and were more often on P2Y₁₂ inhibitors and aspirin at discharge but less often on beta-blockers (Figure 1A). In multivariable analyses compared with countries in the highest tertile of

FIGURE 1 Treatment of Patients With IHD According to Country Health Care Spending

(A) Bar chart showing the proportion of patients with ischemic heart disease (IHD) undergoing a procedure (percutaneous coronary intervention [PCI]/coronary artery bypass grafting [CABG]) during the index hospitalization and medical therapy received at discharge stratified according to tertiles of country health care expenditure.

(B) Bar chart showing the proportion of patients with IHD undergoing procedures (PCI, CABG) during the index hospitalization and receiving medical therapy at discharge according to insurance status.

health care expenditure (Supplemental Table 5), P2Y₁₂ inhibitors at discharge were more often used in countries in the lowest health care expenditure tertile (odds ratio [OR]: 1.78; 95% confidence interval [CI]: 1.40 to 2.26)), whereas beta-blockers at discharge (OR: 0.30; 95% CI: 0.23 to 0.39) or PCI/CABG during the index hospitalization (OR: 0.57; 95% CI: 0.47 to 0.70) were used less often. The association between country level health expenditure and aspirin or statin use at discharge was no longer significant in multivariable analyses ($p > 0.05$ for both).

When stratified according to patient health insurance status (public/national, private, or uninsured), patients without health insurance less often had beta-blockers but more often P2Y₁₂ inhibitors at discharge (Figure 1B). PCI/CABG during hospitalization was less common in patients without health insurance compared with patients with health insurance. In multivariable analyses, patients without insurance were less likely on beta-blockers at discharge (OR: 0.61; 95% CI: 0.41 to 0.90) or underwent PCI/CABG during the index hospitalization

FIGURE 2 1-Year Mortality of Patients With and Without IHD

(A) Kaplan-Meier curve showing the cumulative mortality within 1 year stratified according to ischemic heart disease (IHD) status.

(B) Cumulative incidence curve showing cardiovascular (CV) mortality within 1 year stratified according to IHD status.

(OR: 0.35, 95% CI: 0.18 to 0.67) (Supplemental Table 6).

OUTCOME. At 1 year, 3,461 (20%) patients died, and 470 (2.7%) patients were lost to follow-up. Patients without IHD were more often lost to follow-up ($n = 260$ [3%]) compared with patients with IHD

($n = 210$ [2%]). Within 1 year, 1,958 (21%) patients with IHD died compared with 1,500 (18%) patients without IHD (Table 2, Figure 2). In multivariable analyses, patients with IHD were more likely to die within 1 year compared with patients without IHD (hazard ratio [HR]: 1.12; 95% CI: 1.03 to 1.21). Patients

TABLE 3 Cox Regression Analyses

	No IHD	IHD
All-cause death		
Cases/total cases	1,500/8,301	1,958/9,317
Events/100 patient-yrs	20.3 (19.3–21.4)	24.1 (23.0–25.2)
Univariable	Ref.	1.18 (1.09–1.29), <0.001
Model 1		1.10 (1.01–1.20), 0.028
Model 2	Ref.	1.08 (0.99–1.18), 0.060
Model 3	Ref.	1.12 (1.03–1.21), 0.010
MAGGIC risk score	Ref.	1.06 7 (0.98–1.16), 0.129
CV death		
Cases/total cases	870/8,301	1,205/9,317
Events/100 patient-yrs	11.8 (11.0–12.6)	14.8 (14.0–15.7)
Univariable	Ref.	1.25 (1.13–1.39), <0.001
Model 1	Ref.	1.22 (1.09–1.36), <0.001
Model 2	Ref.	1.17 (1.05–1.30), 0.004
Model 3	Ref.	1.21 (1.09–1.35), <0.001
MAGGIC risk score	Ref.	1.14 (1.03–1.27), 0.012
Non-CV death		
Cases/N	235/8,301	284/9,317
Events/100 patient-yrs	3.2 (2.8–3.6)	3.5 (3.1–3.9)
Univariable	Ref.	1.08 (0.90–1.29), 0.417
Model 1	Ref.	0.93 (0.78–1.12), 0.452
Model 2	Ref.	0.97 (0.81–1.17), 0.787
Model 3	Ref.	1.17 (0.84–1.62), 0.346
MAGGIC risk score*	Ref.	0.97 (0.81–1.16), 0.733

Values are hazard ratio (95% confidence interval), p value, unless otherwise indicated. Model 1: Age, sex, history of hypertension; atrial fibrillation; anemia; valvular heart disease. Model 2: Model 1 + region, and HF diagnosis (new onset vs. decompensated chronic heart failure). Model 3: Model 3 + treatment with ACE inhibitors/ARBs, mineralocorticoid receptor antagonists, and beta-blockers and mineralocorticoid receptor antagonists at discharge. *LVEF, systolic blood pressure, age, sex, body mass index, creatinine, NYHA functional class, history of diabetes or COPD, time since diagnosis, use of ACE inhibitors/ARBs at discharge, and use of beta-blockers at discharge.

CV = cardiovascular; HR = hazard ratio; other abbreviations as in Table 1.

with IHD were more likely to die from CV causes compared with those without (HR: 1.21; 95% CI: 1.09 to 1.35) (Table 3). No significant association with non-CV mortality was observed. After correction for the MAGGIC risk score, IHD was significantly associated with CV death (HR: 1.14; 95% CI: 1.03 to 1.27; $p = 0.012$) but not with all-cause ($p = 0.129$) or non-CV ($p = 0.733$) death. Patients with IHD were more likely re-hospitalized for HF (23% vs. 21%) despite the competing risk of higher all-cause death. In total, 734 (4%) patients had new-onset CAD during follow-up, which was more common in patients with IHD ($n = 557$ [6%]) than without IHD ($n = 177$ [2%]).

Patients with a history of IHD alone (HR: 1.12; 95% CI: 1.03 to 1.22; $p = 0.01$) but not new-onset IHD (HR: 0.96; 95% CI: 0.84 to 1.09; $p = 0.489$) had worse 1-year all-cause mortality after correcting for the MAGGIC risk score (Supplemental Table 7). The association between a history of IHD alone and CV death remained significant (HR: 1.19; 95% CI: 1.07 to 1.32; $p = 0.002$). The association between new-onset

IHD and CV death was not significant ($p = 0.563$) after correction for the MAGGIC risk score.

We found an interaction between HF subtype (i.e., HFrEF, HFmrEF, HFpEF) and IHD status for 1-year mortality ($p_{\text{interaction}} < 0.001$), such that IHD was associated with higher CV mortality in patients with HFrEF (HR: 1.20; 95% CI: 1.05 to 1.36; $p = 0.006$) but not with HFpEF (HR 0.95; 95% CI: 0.77 to 1.16; $p = 0.592$) (Supplemental Table 8). The interaction remained significant after correction for the MAGGIC risk score ($p_{\text{interaction}} < 0.001$). When restricting the test for interaction to patients with LVEF measured during the index hospitalization, significance remained ($p_{\text{interaction}} < 0.001$). After correcting for treatment indication bias, being on beta-blockers, statins, or aspirin at discharge was associated with a reduction in mortality in patients with IHD (Supplemental Table 9).

DISCUSSION

In the largest global cohort of patients with acute HF to date, 53% of patients admitted for AHF had IHD, and 17% were admitted with new-onset IHD. IHD was more common in lower income countries, particularly Eastern Europe and Southeast Asia. Patients from countries with lower health care expenditures, and patients without health insurance, were more often undertreated and less likely underwent cardiac revascularization. Finally, IHD was associated with worse post-discharge mortality, especially in HFrEF. These data highlight the increasing burden of IHD in patients hospitalized for AHF from lower income regions and suggest that efforts to improve quality of treatment are warranted.

In REPORT-HF, there was substantial regional variation in prevalence of IHD, which was most common in Southeast Asia and Eastern Europe. Many of the countries included in these regions are currently undergoing rapid economic development and population growth. Indeed, the age-standardized death rate due to IHD is increasing in many locations across south, east, and southeastern Asia, including China and India (14). This also holds true for patients with HF: CAD was present in 54% of Indian patients and up to 50% of Chinese patients in the ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry (15). In INTER-CHF, IHD was present in 46% of Indian participants, 56% of Southeast Asian participants, and 45% of patients from China (6). Although REPORT-HF included few countries from the Middle East, in the Gulf CARE (Gulf Acute Heart Failure) registry, CAD was the primary etiology in more than one-half of patients admitted for AHF (16), and in

Pakistan up to 77% of patients have IHD (17). Changing lifestyles, rapid economic development, and a higher exposure to risk factors, including air pollution, high-fat diet, tobacco smoking, and excessive alcohol use, might partially explain these findings. Although no data were available in REPORT-HF on countries from sub-Saharan Africa, hypertensive heart disease was more common than IHD in INTER-CHF and THESUS-HF (Sub-Saharan Africa Survey of Heart Failure) (6,18). Results of the current study are best valued in light of the sampling strategy of REPORT-HF. The number of centers per country took into account the size of its population. However, priority was given to sites that could provide high-quality data, with little missingness. Given the limitations of performing these large-scale cohort studies, especially in countries with heterogeneous health care systems, our data likely represent a best-case scenario for many countries. This might introduce selection bias and underestimate broader deficiencies in IHD care.

Evidence in support of the association between economic factors and measures of treatment quality and use in CV disease is substantial (19–21). In the PURE (Prospective Urban Rural Epidemiology) study, use of aspirin, statins, ACE inhibitors/ARBs, β -blockers, and antiplatelets decreased with a decrease in country-level gross domestic product in patients at high risk for CV disease (21). In the ASIAN-HF and INTER-CHF studies, use of ACE inhibitors/ARBs, β -blockers, and mineralocorticoid receptor antagonists was lower in lower income countries (6,22). CABG/PCI during the index hospitalization was less common among patients without health insurance and patients from countries with low health care expenditure. Surprisingly, lower health care spending was associated with higher use of P2Y₁₂ inhibitors, which was not explained by differences in health care facilities. The patent on clopidogrel expired in 2012 (23), opened up the market up to cheaper generic versions. This is combined with fewer coronary revascularizations, which might lead to preferring medical treatment over interventions; however, this deserves further study. Together, this highlights the importance of socioeconomic factors in determining treatment of IHD.

IHD was associated with worse 1-year mortality, especially in patients with HFrEF. This finding confirms earlier results from several large registries and post hoc analyses of randomized clinical trials (1–3). The reoccurrence of MI/ACS within 1 year was low in REPORT-HF, with <1% of patients without reporting a new MI/ACS during 1-year follow-up and only 2% of patients with IHD. This might be partially explained

by underreporting of participants and/or investigators. Furthermore, these events were not adjudicated. In the SwedeHF (Swedish Heart Failure) registry, IHD was associated with an equally high risk for new IHD events across ejection fraction subtypes. However, IHD conferred a higher risk for all-cause mortality in patients with HFrEF compared with patients with HFpEF (1). In the Framingham Heart Study, IHD was associated with worse outcomes in patients with HFrEF compared with those with HFpEF (24). We found a similar interaction between left ventricular subtype and IHD for CV mortality, such that IHD was associated with a lower relative risk for CV death in patients with HFpEF compared with patients with HFrEF. This difference might be explained by the differences in proportion of deaths attributable to CV causes in patients with HFpEF and HFrEF¹. Notably, this highlights a possible divergent role of IHD in patients with HFrEF and HFpEF, such that in patients with HFrEF, IHD might be a direct cause of ischemic left ventricular dysfunction and myocardial cell loss, whereas in HFpEF, IHD plays a more complex role involving other comorbidities and mechanisms mediated by coronary microvascular and diastolic dysfunction (25).

STUDY LIMITATIONS. REPORT-HF reflects real-world practice and shows differences in practice determined by locally available resources. For practical reasons, we did not take a random sample of countries or of clinical sites within a country. This may have led to possible selection bias regarding centers included in this study. Patients in lower income countries with IHD might be less likely to make it to a hospital, which can cause survival bias in the inclusion of participants. Values for plasma natriuretic peptides were not available in a large number of patients and were not included in our multivariable models. Because the aim of REPORT-HF was to study differences in health care practices and treatment for AHF, diagnosis of AHF was made at the discretion of the local investigator, and measurement of natriuretic peptides was not mandated. Patients had to provide informed consent, which potentially might select more stable patients and might explain the low index hospitalization mortality. Hence, investigators might not have enrolled sicker, frailer patients.

Because ethnicity and region were largely collinear in REPORT-HF, we could not include both variables in our prediction models. In North America, many of the sites chosen served predominantly African-American patients, who develop HF at a younger age and have worse prognosis compared with patients of European descent. Although this is the largest global study on

acute HF to date, REPORT-HF did not include patients from sub-Saharan Africa, and the global proportion of Black patients is therefore relatively low. Data in REPORT-HF might not be reflective of populations seen in predominantly rural facilities and the rural poor, especially in sub-Saharan Africa. Time to hospitalization and recurrent ischemic events was not available, and thus we could not correct for the competing risk of mortality. Lastly, outcomes, cause of death, and cause of hospitalization were determined by the investigator and were not independently adjudicated.

CONCLUSIONS

IHD is common in patients hospitalized with AHF. The burden of IHD is greatest in patients from Eastern Europe and Southeast Asia. IHD in patients with AHF was associated with higher 1-year mortality, especially in patients with HFrEF, regardless of region. Despite greater mortality, patients with IHD from regions with lower health care expenditure, and patients without health insurance were less likely treated with β -blockers and PCI/CABG. Initiatives are required to improve the implementation of life-saving therapies globally, especially in vulnerable patient-groups in low-income countries.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The prevalence of IHD among patients hospitalized for HF is greater in lower income compared with high-income countries and associated with worse outcomes. Patients in countries with lower health care expenditure per capita and patients without health insurance were less likely to undergo coronary revascularization or be prescribed anticoagulants.

TRANSLATIONAL OUTLOOK: Patients with HF in regions with the greatest burden of IHD are more commonly undertreated. These data highlight the need for initiatives to improve the implementation of life-saving therapies globally, especially in lower income countries.

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APPENDIX For supplemental tables, please see the online version of this paper.